Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Safety profile of the antiviral drug remdesivir: An update

The expanding epidemic of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has posed a serious threat to the global public health. There is an urgent demand for safe and effective therapeutics. Remdesivir, a broad-spectrum antiviral drug, emerges as a potential candidate for fighting against COVID-19 because of its potent in vitro anti-SARS-CoV-2 activity [1] and encouraging benefits for the infected patients [2]. However, with increasing application, adverse effects of remdesivir have been detected and become a concern of clinicians. Since current safety data about remdesivir is fragmented and limited, we reviewed published studies and official documents regarding remdesivir treatment and summarize the up-to-date safety information, especially in COVID-19 patients (Table 1), to provide evidence for clinical practices.

Hepatotoxicity. Toxicity studies of remdesivir in animals showed no liver changes, while transient treatment-emergent elevations in aminotransferases were noticed in clinical studies of remdesivir [3]. In a case series, increased aminotransferases following remdesivir initiation were observed in three COVID-19 patients [4]. Lescure et al. also reported one COVID-19 patient discontinued remdesivir because of alanine aminotransferase elevation and rash, which then decreased within 3 days [5]. According to Grein et al.'s study on compassionate-use remdesivir against COVID-19, 23 % of the patients reported increased hepatic enzymes, and two of them therefore discontinued remdesivir prematurely [2]. A recent randomized controlled trial (RCT) in China also showed that total bilirubin, aspartate and alanine aminotransferase increased, respectively, in 10 %, 5 % and 1 % of COVID-19 patients in the remdesivir group versus 9 %, 12 % and none of COVID-19 patients in the placebo group [6]. More patients in the remdesivir group than the placebo group discontinued the study drug because of aminotransferase or bilirubin increases [6]. However, it should be noted that frequent incident liver injury was observed in COVID-19 patients [7], therefore it is challenging to distinguish whether the elevations in aminotransferases and/or bilirubin attributed to remdesivir or to the underlying diseases. As recommended by European Medicines Agency, remdesivir should not be used with other hepatotoxic drugs and hepatic function monitoring is required during the treatment [8]. Since most COVID-19 patients with liver injury had mild aminotransferases and/or bilirubin increases [7], if abnormality of liver enzymes occur after remdesivir initiation, especially in high levels, adverse drug reactions need to be considered and drug discontinuation is required if necessary.

Gastrointestinal symptoms. According to a case series in which three COVID-19 patients were treated with remdesivir, two had nausea and one suffered from gastroparesis after the treatment initiation [4]. Diarrhea was observed in 9 % of the remdesivir recipients in Grein et al.'s study [2]. Based on a RCT in China, a higher proportion of remdesivir recipients than placebo recipients had dosing prematurely stopped because of anorexia, nausea, and vomiting [6].

Respiratory toxicity. Safety studies of remdesivir in animals showed no adverse effects on respiration except for transiently increased respiration rates [3]. However, acute respiratory distress syndrome (4 %) and pneumothorax (4 %) were reported after the infusion of remdesivir in Grein et al.'s study [2]. Based on the findings from a RCT in China, more patients in the remdesivir group than the placebo group suffered from respiratory failure or acute respiratory distress syndrome (10 % versus 8 %) and therefore discontinued the study drug (5 % versus 1 %) [6].

Cardiovascular toxicity. No side effect of remdesivir on cardiovascular parameters was observed in safety studies on monkeys [3]. However, one case of hypotension was judged to be potentially related to remdesivir in a RCT of experimental therapies against Ebola [9]. In Grein et al.'s study, hypotension (8 %), atrial fibrillation (6 %) and hypernatremia (6 %) were observed in COVID-19 patients treated with remdesivir [2]. What is more, one case of cardiac arrest was reported in remdesivir group in a RCT in China [6].

Nephrotoxicity. Although there was no evidence of remdesivir-related nephrotoxicity in Phase I clinical studies, dose-dependent kidney injury and/or reduced function was detected in the repeated dose toxicity studies of remdesivir in animals, which correlated with histopathology findings of renal tubular atrophy, basophilia and casts [3]. Grein et al. reported renal impairments, acute kidney injury and hematuria in 8 %, 6 % and 4 % of the remdesivir recipients, respectively [2]. A COVID-19 patient, who was treated by our team in Wuhan in March 2020, suffered from acute renal failure after using remdesivir. This case was also reported in a RCT in China [6]. Therefore, it is important to monitor kidney function during remdesivir treatment, particularly for those with pre-existing renal impairments or those receiving combination therapies with other nephrotoxins.

Reproductive toxicity. Reproductive and development toxicity studies in animals revealed remdesivir had no effect on reproductive functions in males or on embryo-fetal and peri-postnatal development, but effect on fertility parameters in female rats were notably found [3]. Although it is not recommended to use in pregnant women, remdesivir treatment is necessary in some cases after weighing the pros and cons. Based on previous application against Ebola, remdesivir appears to be safe in human pregnancies [9]. However, the safety of remdesivir in this special group of patients needs to be further evaluated by therapeutic trials which include pregnant women of COVID-19.

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Table 1
Summary of main adverse events in COVID-19 patients treated with remdesivir.

Adverse events	Clinical studies	No. of adverse events/ No. of remdesivir recipients
Hepatotoxicity		
Hepatic enzyme increased*	J. Grein, et al. [2] [a]	12/53
	Y. Wang, et al. [6] [a]	15/155 (TB increased)
		7/155 (AST increased)
		2/155 (ALT increased)
	The COVID-19 Investigation Team [4] [b]	3/3
	F.X. Lescure, et al. [5] [b]	1/3
Gastrointestinal symptoms		
Constipation	Y. Wang, et al. [6] [a]	21/155
Nausea	Y. Wang, et al. [6] [a]	8/155
	The COVID-19 Investigation Team [4] [b]	2/3
Diarrhea	J. Grein, et al. [2] [a]	5/53
	Y. Wang, et al. [6] [a]	5/155
Vomiting	Y. Wang, et al. [6] [a]	4/155
Poor appetite	Y. Wang, et al. [6] [a]	1/155
Gastroparesis	The COVID-19 Investigation Team [4] [b]	1/3
Respiratory toxicity		
Respiratory failure or acute respiratory distress syndrome	J. Grein, et al. [2] [a]	2/53
	Y. Wang, et al. [6] [a]	16/155
Pneumothorax	J. Grein, et al. [2] [a]	2/53
Cardiovascular toxicity		
Hypotension	J. Grein, et al. [2] [a]	4/53
Atrial fibrillation	J. Grein, et al. [2] [a]	3/53
Hypernatremia	J. Grein, et al. [2] [a]	3/53
Cardiac arrest	Y. Wang, et al. [6] [a]	1/155
Nephrotoxicity		
Renal impairments	J. Grein, et al. [2] [a]	4/53
Acute kidney injury	J. Grein, et al. [2] [a]	3/53
	Y. Wang, et al. [6] [a]	1/155
Hematuria	J. Grein, et al. [2] [a]	2/53

TB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] Clinical trial.
[b] Case series.
* Hepatic enzyme increased includes the following terms: hepatic enzyme increased, ALT increased, AST increased and transaminases increased.

Other adverse effects. Transient rise in serum amylase was reported in an Ebola-infected patient treated with remdesivir [10]. Grein et al.'s study mentioned rash, multiple-organ-dysfunction syndrome, deep-vein thrombosis, delirium, septic shock, pyrexia as adverse events occurred in remdesivir recipients [2]. Adverse events related to hematologic, circulatory, endocrine and other systems were also detected in the remdesivir group in the RCT in China [6].

The current safety profile of remdesivir is still incomplete. Increasing evidence has witnessed COVID-19 is implicated in injuries of multiple organs including lung, liver, gastrointestinal tract, heart and kidney [7,11–13], hence it is complex to distinguish the underlying causes of adverse events during remdesivir treatment. Moreover, the latest safety data from Grein et al.'s study on compassionate-use remdesivir which reported adverse events in 60 % of the patients and the RCT in China which reported adverse events in 66 % of remdesivir recipients versus 64 % of placebo recipients might be limited by the inclusion criteria, finite sample size and follow-up duration. Since the experience of remdesivir application in the newly emerging COVID-19 is still limited, adverse drug effects need to be paid much attention to.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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Qianqian Fan, Bo Zhang
Department of Pharmacy, Peking Union Medical College Hospital, Beijing 100730, China

Jie Ma*
Department of Nephrology, Peking Union Medical College Hospital, Beijing 100730, China
E-mail address: majie6497@163.com.

Shuyang Zhang**
Department of Cardiology, Peking Union Medical College Hospital, Beijing 100730, China
E-mail address: shuyangzhang103@163.com.

* Corresponding author at: Department of Nephrology, Peking Union Medical College Hospital, No.1 Shuaifuyuan, Dongcheng District, Beijing 100730, China.
** Corresponding author at: Department of Cardiology, Peking Union Medical College Hospital, No.1 Shuaifuyuan, Dongcheng District, Beijing 100730, China.